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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/988,115 | 11/16/2001 | James M. Robl | 50195/008003 | 8075 |

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| EXAMINER | |
|---|---|
| CROUCH, DEBORAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/988,115 | ROBL ET AL. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *6-9,15-20,22,27 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10-14,21,23-26,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of group I, claims 1-5, 10-14, 21, 23-26, 28 and 29 in the reply filed on April 12, 2004 is acknowledged. Pending claims are 1-32. Claims 6-9, 15-20, 22, 27 and 30-32 are withdrawn as being to a nonelected invention. Claims 1-5, 10-14, 21, 23-26, 28 and 29 are examined in this office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 10-14, 21, 23-26, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are to a transgenic ungulate comprising nucleic acids encoding all or part of a xenogenous immunoglobulin (Ig) gene which undergoes rearrangement and expresses more than one xenogenous Ig molecule, an ungulate somatic cell comprising nucleic acids encoding all or part of a xenogenous Ig gene which undergoes rearrangement and expresses more than one xenogenous Ig molecules in B cells, methods of producing antibodies comprising administering one or more antigens to the ungulate wherein the gene undergoes rearrangement resulting in the production of antibodies specific for said antigens and recovering the antibodies from the ungulate, and methods of producing antibodies comprising recovering antibodies from the ungulate where a nucleic acid encoding a xenogenous antibody gene locus undergoes rearrangement resulting in the production of antibodies.

To refer to "immunoglobulin gene" is a misnomer. In humans, and presumably other nonungulate species, immunoglobulin proteins are located on different chromosomes. In humans, as stated in the specification, the locations are chromosomes 14 and 22. The proper term to use is "immunoglobulin locus." "Immunoglobulin gene" is not enabled because there is not a gene for each antibody found in a person or nonungulate's repertoire. The immunoglobulin locus undergoes rearrangement during B-cell maturation to produce a chromosomal locus which encodes an antibody sequence for each antigen. Furthermore, there is no enablement for part of xenogenous Ig gene as there is no guidance on the parts of the gene needed for antibody production. In addition, the vector used to introduce the Ig locus is critical to the production of the claimed ungulates and ultimately the production of xenogeneic antibodies. The Ig locus is very large, and cannot be microinjected alone into a cell because of DNA shearing effects. Rather, the production of the ungulates would necessarily require some artificial chromosome or micro cell type vector. Claims not so limited, such as claims 1-3, are not enabled.

The claims are not enabled because the specification does not provide evidence or guidance that an ungulate can produce xenogeneic antibodies and in particular does not provide evidence or guidance for the production of human antibodies. Cows, sheep and pigs have a relatively small number of functional germ line V-genes, which imposes constraints in the generation of antibody diversity as compared with animals such as humans and mice that possess a large pool of divergent VDJ genes that cause significant diversity. In sheep and bovines, antibody diversity takes place in the Ileal Payer's patches, where somatic hypermutations take place during B cell development (see Parng, pages 5478 and 5479). Sheep and bovine B cells develop without the influence of maternal antibodies, and selective forces operating during B cells development are different from those observed in mice and humans where maternal antibodies influence the developing B cell repertoire. (see Kaushik,

pages 347 and 348, col. 1). Thus, it is not clear that a human or other nonungulate antibody locus would undergo rearrangement and develop even immature B-cells under the mechanism found in the Ileal patch, or that that B-cells maturation would occur responsive to a particular antigen. In humans, B-cells are made in the bone marrow and travel to the lymph nodes for maturation into particular antibody secreting cells. The B-cells reaching the lymph node are committed to a certain antibody lineage. Since the B-cell maturation process is so very different from that found in humans, for example in claim 2, it is very likely that antibody diversity would not be found or that no antibodies would be produced.

The specification specifically discloses the production of transgenic bovine fetuses comprising a human artificial chromosome containing the human Ig locus. However, artificial chromosomes are known to be unstable, and that they lose their genomic content in a random, unpredictable manner. While the specification states that one transgenic calf was born, there is no analysis of the calf to determine if the HAC remains faithful and is rearranged to product Ig protein alone or a specific Ig in response to a particular antigen.

It should also be noted that the claimed ungulate will be expressing a nonungulate Ig locus on the ungulate Ig background. Thus, any antibody that contains a nonungulate Ig polypeptide would inherently be a hybrid ungulate - nonungulate antibody. The specification discloses the claimed ungulate and the methods of producing antibodies for purposes of disease treatment. However, the hybrid antibody will cause an immune response when administered. For example, the bovine portion of a human-bovine antibody will itself induce an immune response when administered to a human. The net result of the immune response to the antibody is prevention of the antibody reaching its target and clearing the targeted antigen. For the purposes disclosed, there is no use for a hybrid antibody.

Thus, at the time of filing the skilled artisan would have been required to perform an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 10-14, 21, 23-26, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over U. S. Patent 5,569,825 issued October 29, 1996 (Lonberg) in view of U.S. Patent 5,741,957 issued November 19, 1999 (Deboer).

Lonberg teaches the production of transgenic mice comprising an unrearranged human heavy chain Ig minilocus comprising human VH gene segments, a plurality of human D gene segments, a plurality of JH gene segments a mu constant regions comprising a mu switch regions, a gamma constant region comprising a gamma switch region (col. 44, lines 23 to col. 45, line 60). The mouse was produced by the microinjection of a YAC vector comprising the DNA construct into a fertilized mouse zygote. The mouse is taught to express both IgM and IgG antibodies (col. 50, lines 25-47). Lonberg states that the bovine, ovine and porcine species are contemplated as other transgenic species for the production of human or other species antibodies (col. 10, lines 57-58).

Deboer teaches the production of transgenic bovines by the microinjection of a DNA construct comprising a milk protein gene promoter operatively linked to a DNA sequence encoding a protein of interest into bovine fertilized zygotes (col. 15, line 52-64). Deboer

further teaches that heterologous antibodies can be isolated from the milk of the bovine (col. 7, lines 11-15).

Motivation is provided by Lonberg stating that the human antibodies produced by transgenic mammals would obviate the immune response generated when nonhuman antibodies are administered to a human (col. 1, lines 30-38).

Thus, at the time of the instant invention it would have been obvious to the ordinary artisan to produce transgenic bovines comprising a human Ig mini-gene locus given Lonberg teaching of mice transgenic for a human Ig mini-gene locus made by microinjection of the mini-gene locus into mouse fertilized eggs, cells from the bovines, and producing human antibodies in view of DeBoer teaching methods for producing transgenic bovines by microinjection of a DNA construction into bovine zygotes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632/1630

July 26, 2004